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Randomized, Crossover, Non-Inferiority Study to Evaluate the Efficacy, Safety and Tolerability of Two Budenoside/ Formoterol Fumarate Formulations in Asthmatic Adults

Estudio aleatorizado, cruzado, de no inferioridad para evaluar la eficacia, la seguridad y la tolerabilidad de dos formulaciones de budesonida/fumarato de formoterol en adultos asmáticos

Esquivel Florencia[1]; Costantini Andrea[2]; Maspero Jorge[3]; Simón Gonzalo[2]; Moorat Anne; Mallett Steve

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Correspondence
Florencia Esquivel
E-mail:
floresqui07@yahoo.com.ar

ABSTRACT

Asthma is a serious worldwide health problem. According to the last report of the Ministry of Health, 1,380,000 subjects suffer from asthma in Argentina. The International Guidelines (Europe, United States, WHO [World Health Organization]) have varying approaches to define equivalence considerations and the possibility of switching orally inhaled products. Whereas an *in vitro* approach is possible, in general the Guidelines recommend providing more clinical evidence that supports the possibility of switching from the innovative product to another one subsequently developed with the same active principles in the form of dry powder inhaler. This randomized, phase IV study has been conducted to establish the efficacy, safety and tolerability of Neumoterol® 400 compared to the reference medicinal product Symbicort forte, budenoside/formoterol fumarate 320/9 µg twice daily in asthmatic patients. Also, the patients' preference on the use of the devices has been evaluated.

The evaluated formulation has proven to be non-inferior compared to the reference medicinal product. The lower limit of the 95% CI (confidence interval) for the treatment difference was greater than the prespecified non-inferiority margin of –125 mL (difference: 0.044 l [95% CI: –0.008 to 0.096]). Also, higher values were evidenced for the $AUC_{0\text{-}10h}$ (area under the curve) of the FEV_1 (forced expiratory volume in the first second) and a more important change of the baseline score in the asthma control test on day 29 for the budenoside/formoterol fumarate capsules of 400/12 µg. In one exploratory test about the patients' preference on the use of the devices, a higher proportion of participants expressed their global preference for the budenoside/formoterol fumarate capsule of 400/12 µg. No differences were reported in the incidence of AEs (adverse events) or SAEs (serious adverse events) during or after the treatment. The safety profile of both products in general coincides with the verified profile of budenoside/formoterol fumarate.

Key words: asthma; budenoside; formoterol fumarate; inhalation device.

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[1] Laboratorios Phoenix SAICF
[2] GlaxoSmithKline Argentina
[3] CIDEA Argentina

RESUMEN

El asma es un grave problema de salud mundial. Según el último informe del Ministerio de Salud, 1 380 000 sujetos padecen asma en la Argentina. Las guías internacionales (Europa, Estados Unidos, OMS) varían en su enfoque para definir la equivalencia y la posibilidad de intercambio de los productos para inhalación respiratorios. Si bien es posible un enfoque *in vitro*, en general las guías recomiendan brindar más indicios clínicos que avalen la posibilidad de intercambiar el producto innovador por otro posteriormente desarrollado con iguales principios activos en polvo seco para inhalar. Este estudio, aleatorizado de fase IV, se realizó para establecer la eficacia, seguridad y tolerabilidad de Neumoterol® 400 en comparación con el producto medicinal de referencia Symbicort forte budesonida/fumarato de formoterol 320/9 µg, indicados 2 veces al día en pacientes asmáticos. Además, se evaluó la preferencia de los pacientes por uno u otro dispositivo.

Se demostró la no inferioridad de la formulación evaluada en comparación con el producto medicinal de referencia. El límite inferior del IC del 95 % para la diferencia entre los tratamientos fue mayor que el margen predefinido de no inferioridad de –125 mL (diferencia: 0,044 l [IC del 95 %: –0,008 a 0,096]). Asimismo, se comprobaron valores más altos para el $AUC_{0\text{-}10h}$ del FEV_1 y un mayor cambio respecto del puntaje basal en la prueba de control del asma el día 29 para las cápsulas de budesonida/fumarato de formoterol 400/12 µg. En un análisis exploratorio sobre la preferencia de los pacientes por los dispositivos, una mayor proporción de participantes expresaron su preferencia global por la cápsula de budesonida/fumarato de formoterol 400/12 µg. No se informaron diferencias en la incidencia de AE o SAE graves durante el tratamiento o después de este. El perfil de seguridad de ambos productos en general concordó con el perfil comprobado de budesonida/fumarato de formoterol.

Palabras clave: Asma; budesonida; fumarato de formoterol; dispositivo inhalatorio

INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways, characterized by hyperreactivity of the airway that produces recurring episodes of sibilance, shortness of breath and cough, especially at night or early in the morning. It is a high-prevalence disease and represents an important public health problem.[1, 2]

The guidelines of the Global Initiative for Asthma (GINA) highlight the need to treat the inflammation of the airways in asthma, and also to acknowledge the importance of prophylactic inhaled drugs, such as inhaled corticosteroids (ICS) and the combinations of ICS/βlong-acting beta-adrenergic agonists (LABA) (also called long-acting β-2 agonists), like the product containing the budenoside/formoterol fumarate combination (BFF).[2]

Symbicort forte® (with turbuhaler® inhaler) was authorized in 2010 in Argentina for the treatment of asthma and chronic obstructive pulmonary disease (COPD).[3]

Phoenix laboratory developed Neumoterol® 400, a combination of a fixed-dose of BFF dry powder (DPI), in capsules, to be administered by means of a single-dose inhaler provided by the Plastiape Company. This formulation consists of a capsule containing a small amount of powder with a mixture of 400 μg of micronized budenoside, 12 μg of micronized formoterol fumarate and excipients. It is indicated as maintenance therapy against asthma and to treat patients suffering from COPD. The International Guidelines from Europe, the United States and the WHO, for example, have varying approaches regarding equivalence considerations and the possibility of switching orally inhaled products. Whereas an *in vitro* approach is possible, in general the Guidelines recommend providing more clinical evidence that supports the possibility of switching between different formulations of the same active principles. However, in areas with emerging markets, the regulatory approach of providing commercial licensing for respiratory inhalers is generally based on the establishment of pharmaceutical equivalence only through an *in*

vitro analysis. In the case of Argentina, the BFF capsule (Neumoterol® 400) was approved only basing on *in vitro* evidence.

This phase IV study was conducted to show the non-inferiority (primary objective), and gather scientific evidence about the efficacy, safety and tolerability, and also to show the patients' preference for the BFF 400/12 μg capsule (Neumoterol®) in comparison with the reference medicinal product (RMP) BFF 320/9 μg (Symbicort forte®) in asthmatic patients.

METHODS

Study design

A phase IV, multicentric, open, randomized, double-crossover, non-inferiority study to compare the efficacy, safety and tolerability of Neumoterol® 400 (BFF 400/12 μg) administered through its specific inhaler, and the RMP, Symbicort forte® (BFF 320/9 μg) administered through the turbuhaler® device in adult asthmatics. (Figure 1)

The study was carried out in accordance with the Good Clinical Practice (GCP) and the International Council for Harmonization (ICH) and all current requirements related to subjects' confidentiality, apart from the ethical principles detailed in the Declaration of Helsinki of 2008. We obtained written informed consent of each subject before specific study procedures were performed.

The study was divided in six phases: prescreening, screening/run-in (4 weeks), treatment period 1 (4 weeks), washout (at least, 4 weeks), treatment period 2 (4 weeks) and follow-up (1 week). The total duration for each subject was at least 17 weeks. The schedule included up to six visits and one follow-up phone call.

At the prescreening visit, informed consent was obtained before performing any procedure or making changes in the dosing regimen of each participant. During prescreening, patients were instructed about the screening and run-in visit. During visit 1 (screening and run-in), subjects who met the inclusion criteria began a run-in period of 4 weeks. Tables 1 and 2 provide information about inclusion and exclusion criteria.

During both the run-in and washout periods, all the subjects received 400 μg of budenoside as DPI, twice a day. All the participants were allowed to use rescue medication (pressurized metered-dose inhaler of salbutamol 100 μg) during the course of the study, until visit 5.

At the end of the run-in period, the patients were re-evaluated; each subject was told to self-administer the study medication in each treatment period during 4 weeks, in the following way, taking into account the randomization schedule:

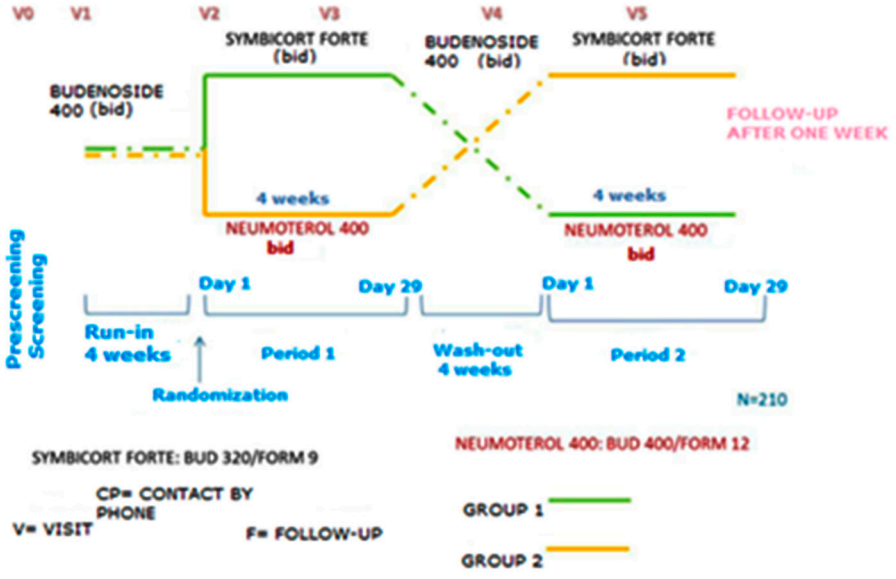

Figure 1. Study design.

TABLE 1. Inclusion criteria

Men or women (18 to 80 years old) with asthma diagnosis at the time they signed the informed consent. Participants were eligible as long as they didn't have reproductive potential, or, if they did, they had to agree to be abstinent or to use contraceptives during an adequate period of time.
Severity of the disease: A better FEV1 (forced expiratory volume in the first second) before using the bronchodilator, of 40% to 85% of the normal predicted value at visit 1 (the predicted percentage was calculated using the reference equations of the Global Lung Function Initiative of the European Respiratory Society)[5]
Reversibility of the disease: Evidenced reversibility of the FEV1 of ≥12% and ≥200 mL in a lapse of 10 to 40 min after 2 to 4 inhalations of salbutamol aerosol (or similar nebulization treatment with salbutamol solution) at visit 1.
Current treatment against asthma: Every subject should have been receiving one ICS ± LABA for at least 8 weeks and a stable dose for at least 4 weeks before visit 1. Two populations were eligible for enrollment: a) participants who received monotherapy with ICS (budesonide 400 µg to 800 µg, twice daily or similar) for at least 8 weeks and a fixed-dose for at least 4 weeks before visit 1 or b) subjects who received a combination product of ICS/LABA for at least 8 weeks and a fixed-dose for at least 4 weeks before visit 1 (screening and run-in visit). The subjects who received BFF as required started to get a maintenance dose (except for the highest dose) using a short-acting beta-adrenergic drug to alleviate the symptoms for at least 8 weeks and a fixed-dose for at least 4 weeks before visit 1. Subjects receiving monotherapy with a low dose of ICS had to enroll only if, after reviewing their medical records and performing a clinical examination, the investigator thought they could benefit from an increase in the ICS dose and the incorporation of a LABA therapy, by using a ICS/LABA combination.
Capacity to suspend LABA therapy: Except for what it provided during the study, the LABA therapy wasn't allowed neither at visit 1 nor during the study. The last dose of the LABA and LABA/ICS combinations before the study had to be taken the day before visit 1. According to the criterion of the investigators, participants had to be able to suspend LABA therapy during the run-in and washout periods.
Short-acting beta-adrenergic drug: All the subjects had to be able to replace their current treatment with rescue salbutamol at visit 1, to be used as required throughout the study. Participants had to be able to suspend salbutamol for at least 6 h before every study visit.
Hepatic safety criteria: ALT ≤ 2 x ULN (upper limit of normal), alkaline phosphatase and total bilirubin ≤ 1.5 x ULN (one isolated bilirubin > 1.5 x ULN was acceptable if the bilirubin was fractionated and the direct bilirubin was <35%) at visit 1.
ECG safety criteria: The ECG of the subjects didn't have to show any anomalies that in the investigator's opinion could compromise their safety of significantly affect their capacity to complete the study. So, the investigator determined the clinical significance of any ECG anomaly and if the subject was allowed to be admitted to the study or not. The ECG safety criteria at visit 1 had to be Qtc (corrected QT interval) < 450 ms or QTc < 480 ms for patients with bundle branch block.
The subject or his/her legal tutor (if applicable) had to be able to provide **informed consent/assent**, including the fulfillment of the requirements and restrictions of the study which are mentioned in the consent form.

Abbreviations: ALT: alanine aminotransferase; BFF: budenoside/formoterol fumarate; ECG: electrocardiogram; ICS: inhaled corticosteroids; LABA: long-acting beta-adrenergic drugs. ULN: upper limit of normal.

a) inhalation of one capsule of Neumoterol® 400 (BFF 400/12 μg) through his/her device twice daily, one capsule in the morning and the other one in the evening/night (approximately 12 hours later); b) inhalation of RMP through turbuhaler® (BFF 320/9 μg) twice daily, in the morning and in the evening (approximately 12 hours later). After the washout phase of 4 weeks, the participants began the alternative treatment according to the randomization schedule. The following procedures were carried out: efficacy tests, pharmacodynamic (PD) analyses, patient preference survey on the use of the devices, and safety evaluations.

To participate in the study, eligible subjects were required to show a better forced expiratory volume in the first second (FEV_1) before the use of the bronchodilator between ≥ 40% and ≤ 85% of the normal predicted value during visit 1 (screening and run-in visit). The predicted percentage was calculated using the reference equations of the Global Lung Function Initiative of the European Respiratory Society[5] and applying equations or race adjustments, as appropriate. Disease reversibility was evidenced with the improvement in the FEV_1 (≥ 12% and ≥ 200 mL) in a lapse of 10 to 40 min after 2 to 4 inhalations of salbutamol as aerosol inhaler (or similar nebulization treatment with salbutamol solution). Also, the FEV_1 stability limit was considered as a reference point of the subjects' asthma status at run-in, and was used for the comparison throughout the whole treatment phase to evaluate the safety of the subject. It was calculated at visit 2 as 75% of the best FEV_1 before salbutamol.

Patients were dismissed from the study if they missed a required visit, if they didn't show up for

TABLE 2. Exclusion criteria

History of asthma with life-threatening risk (asthma episodes requiring intubation or associated with hypercapnia, cardiac arrest or hypoxic convulsions) in the last 10 years.
Respiratory infection: viral or bacterial infection, either suspected or documented through culture of upper or lower respiratory system, nasal sinuses or middle ear that hadn't been resolved in a lapse of 4 weeks post-visit 1 and produced a change in asthma control, or if the investigator thought the infection would affect the subject's asthma status or his/her capacity to participate in the study.
Any asthma exacerbation requiring oral corticosteroids in a lapse of 12 weeks before visit 1 or hospitalization with additional asthma treatment during 6 months before visit 1.
Uncontrolled asthma: Asthma control test (ACT) below 15 at visit 1.
Concurrent respiratory disease: subjects weren't supposed to show current evidence of pneumonia, pneumothorax, atelectasis, pulmonary fibrosis disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, COPD or any other respiratory anomalies, except for asthma.
Other concurring diseases/anomalies: subjects weren't supposed to show any uncontrolled condition or clinically significant disease status that in the investigator's opinion would risk the subjects' safety or alter the interpretation of efficacy results, should the condition/disease be exacerbated during the study.
Evidence of severe exacerbation (asthma impairment requiring the use of systemic corticosteroids for at least 3 days, or patient's hospitalization, or a visit to the emergency department because of the asthma, requiring systemic corticosteroids between visits 1 and 2).
Subjects weren't eligible for run-in if they showed clinical visual evidence of candidiasis during visit 1.
Drug research: the subjects shouldn't have received any experimental drug for a lapse of 30 days before visit 1 or after five half-lives of the previously experimental drug (whichever is longer).
Allergies: a) Drug allergy: Any adverse reaction, including immediate or delayed hypersensitivity to any sympathomimetic beta-2-agonist drug or any intranasal, inhaled or systemic corticosteroid therapy; proven or suspected sensitivity to the components of the products used to test BFF or to BFF capsules (for example, lactose); b) History of severe allergy to milk proteins.
Concomitant drugs: Administration of prescribed or over-the-counter medications that would significantly affect the course of asthma or interact with the study treatment, as for example, anticonvulsants (barbiturates, hydantoins, carbamazepin), polycyclic antidepressants, beta-adrenergic blocking agents, phenothiazines and monoamine oxidase inhibitors.
Immunosuppressor medications: The subject shouldn't have been using or shouldn't have needed these medications during the course of the study. Immunotherapy was allowed during the study to treat allergies, as long as it started at least 4 weeks before visit 1 and if subjects remained in the maintenance phase during the course of the study.
Cytochrome P450 3A4 (CYP3A4) inhibitors: Subjects who had received strong CYP3A4 inhibitors in a lapse of 4 weeks from visit 1 (for example, ritonavir, ketoconazole, itraconazole).
The subject wasn't able to abstain from using prescribed or over-the-counter drugs, not even vitamins, or herbal or dietary supplements in a lapse of 7 days (or 14 d if the drug is a potential enzyme inductor) or five half-lives (whichever is longer) before the first dose of the study medication.
Any subject who received omalizumab within a lapse of 12 weeks before visit 1 or if he/she was receiving omalizumab at the time of the study.
Compliance: Subjects weren't eligible if they, their parents or their legal tutors had any illness, disability, disease or any geographic location that could affect the compliance of any aspect of this study protocol, even the visit schedule and daily activities (according to the investigator's opinion).
Smoking condition: Current smoker or smoking history of $\geq$ 10 packs-year; the subject shouldn't have used smoking inhalation products for the last 3 months (for example, cigarettes, cigars or tobacco pipe). "Packs/year" means 20 smoked cigarettes (1 pack) per day for 1 year.
Pregnant women, as determined through urine test at visit 1 or before the first dose. A confirmatory serum pregnancy test was required if the urine test was questionable or positive.
Breast-feeding women.
A positive result in the hepatitis B or C surface antigen test.
Subjects with mental or legal disability.
Unwillingness or inability to follow the procedures detailed in the protocol.

a re-scheduled visit or weren't able to contact the clinic to re-schedule the missed visit. If the participant couldn't be contacted, the case was considered as withdrawal by subject for a primary reason, "lost to follow-up". Furthermore, subjects were dismissed from the study if some of the following criteria were met after taking into account the mean duration of the QTc of electrocardiograms in triplicate: a) QTc > 500 ms; b) QT (not corrected) > 600 ms; c) increase of at least 60 ms compared to baseline QTc.

No privileges or protocol exemptions were allowed, except for immediate safety concerns.

Compliance: The subjects received study treatment at home, except for the morning doses of visits 2 to 5, which they received at the clinic and were observed by the study staff to ensure an adequate administration. Patient compliance was evaluated during clinical visits 3 and 5 and in case of early discontinuation by reviewing the dose counter of the RMP device and counting unused capsules. If the compliance rate was lower than 80% or higher than 120%, the patient was re-educated about the indicated dose. If the treatment was suspended prematurely during the course of the study or the compliance was outside the acceptable range, the Center monitor would be contacted for the purpose of analyzing the subject's eligibility to continue his/her participation in the study.

Patient compliance was also evaluated through a phone call at the end of the second week of each treatment period. The Center physician/staff had shown each subject the procedure for reading the devices accurately before the beginning of the study.

Endpoints: The primary efficacy endpoint was the change in trough FEV_1 in the morning of day 29 in comparison with the baseline value. Trough FEV_1 was defined as the morning prebronchodilator and pre-dose value, 12 hours after last evening dose (day 28), at the end of each treatment period.

The secondary efficacy endpoints included the area under the curve (AUC) of the FEV_1 of 0-10 h at the beginning of each treatment period (0 [before the dose], 5 min, 15 min, 30 min; 1, 2, 5 and 10 h after the morning dose on day 1) and the change in the asthma control test (ACT) score[6] compared to the baseline value after 4 weeks of each treatment period. The equipment used to obtain spirometry measurements either met the minimum performance recommendations of the American Thoracic Society[7] or exceeded them. All the centers used their own spirometry equipment. The highest FEV_1 was recorded after three acceptable efforts. In order to determine the $AUC_{0\text{-}10h}$, the FEV_1 was measured during clinical visits 2 and 4, at 0 (before dose), 5, 10 and 20 min; and 1, 2, 5 and 10 h after the morning dose. The ACT was an autocomplete questionnaire of 5 items which has been developed to measure the subject's asthma control. It could be quickly and easily completed at the clinical practice.[6]

The subject's preference on the use of the devices at the end of each treatment period was defined as an exploratory endpoint. Such preference was analyzed by means of a questionnaire. During visit 3, the participants were asked to complete a survey with 3 questions; during visit 5 (end of study), they completed a survey with 4 questions.

Safety endpoints included the change in vital signs (pulse and arterial pressure) compared to the baseline value, the electrocardiogram and clinical biochemistry tests, the incidence of adverse events (AEs) during each treatment period, the incidence of asthma exacerbations (defined as worsening of asthma that requires treatment other than the treatment of the study or rescue salbutamol; it could even require the use of inhaled or systemic corticosteroids, a visit to the emergency department or hospitalization), the incidence of serious asthma exacerbations (defined as worsening of asthma that requires systemic corticosteroids during at least 3 days, or hospitalization or a visit to the emergency department), the incidence of oral candidiasis evaluated through tests and early discontinuation.

Statistical analysis: Sample size calculations were based on the primary efficacy endpoint. Variability calculations were based on a previous study[8] in which the observed within-subject standard deviation was 210 mL. Assuming said value, 168 subjects would be necessary to show the non-inferiority of the Neumoterol® 400 inhaler (BFF 400/12 μg) and RMP with BFF 320/9 μg twice daily in asthmatic adults, taking into account a true difference of –50 mL with 90% power and a one-sided significance level of 2.5%.

The non-inferiority margin was set at –125 mL according to the minimal clinically important differences (MCIDs) for this population of patients. It has been shown before that MCIDs for a range

of asthmatic patients were 230 mL.[9] In order to consider a withdrawal rate of approximately 10%, the planned number of subjects to be randomized was 187 participants. Around 234 subjects had to be selected and a failure rate of 20% was expected in order to reach 187 randomized subjects and to have 168 subjects completing the study.

An intention-to-treat (ITT) analysis was used for the primary efficacy analysis. A back-up efficacy analysis was carried out using the per-protocol population (PP). Safety analyses were conducted with the safety population. No interim analysis was planned for this study.

The primary efficacy analysis was conducted with a mixed effects analysis of covariance, with the baseline FEV_1, treatment group and period as fixed effects, and the subject as random coefficient. The non-inferiority was evaluated by examining the lower limit of the confidence interval (one-sided significance level of 0.025) and comparing it with the non-inferiority margin of –125 mL. For the secondary endpoints, other comparisons were made between the product of the study (BFF 400/12 μg) administered through a capsule inhaler and the RMP (BFF 320/9 μg). Such comparisons were considered as backup, and no multiplicity adjustments were applied. Current versions of the SAS software were used.

RESULTS

Baseline data

A total of 239 subjects were enrolled in the study, and 199 were randomized (Figure 2). 184 (92%) of the randomized subjects completed the study and 15 (8%) withdrawn from the study. Common reasons for suspension were withdrawal of consent (n = 6; 3%) and protocol deviations (n = 4; 2%). There weren't any withdrawals for lack of efficacy. Table 3 summarizes the distribution of the study subjects according to each treatment period.

All the randomized subjects were included in the safety and ITT population (n = 199) and 158 subjects (79%) were included in the PP population. The demographic characteristics include both groups due to the crossover design of the study. The participants' median of age was 47 years, and

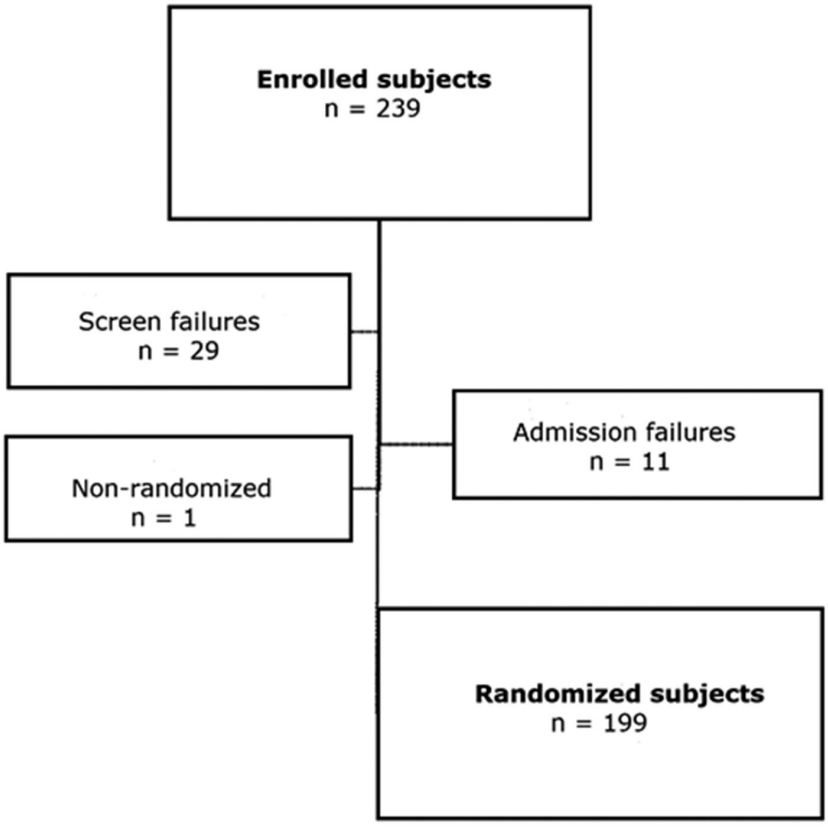

Figure 2. Distribution of subjects.

TABLE 3. Summary of subject distribution (intention-to-treat population)

	Neumoterol® 400 (BFF 400/12 µg) / RMP (BFF 320/9 µg) (n = 100) n (%)	RMP (BFF 320/9 µg)/ Neumoterol® 400 (BFF 400/12 µg) / (n = 99) n (%)	Total (n = 199) n (%)
Completion status			
Completed	93 (93)	91 (92)	184 (92)
Discontinued	7 (7)	8 (8)	15 (8)
Primary reason for discontinuation			
Adverse event	0	1 (1)	1 (1)
Lack of efficacy	0	0	0
Protocol deviation	2 (2)	2 (2)	4 (2)
The subject fulfilled the withdrawal criteria defined in the protocol.	1 (1)	0	1 (1)
Lost to follow-up	1 (1)	1 (1)	2 (1)
Investigator's criterion	1 (1)	0	1 (1)
Withdrawal of consent	2 (2)	4 (4)	6 (3)

TABLE 4. Demographic characteristics (ITT population, n = 199)

Parameter	n (%)
n	199
Mean (standard deviation)	46,2 (15,26)
Median (min., max.)	47 (18; 80)
Age group (years)	
<18	0
18-64	176 (88)
65-74	18 (9)
≥75	5 (3)
Sex	
Female	142 (71)
Male	57 (29)
Reproductive potential of women (*)	
Postmenopausal	56 (39)
Sterile (women of reproductive age)	5 (4)
Potentially capable of having children	81 (57)
Ethnic group	
Hispanic or Latin	165 (83)
Neither Hispanic nor Latin	34 (17)
Race	
White	199 (100)
Body mass index (kg/m^2)	
n	199
Mean (standard deviation)	28,90 (6,378)
Median (min., max.)	28,13 (17,3; 53,0)

(*) Percentages are based on the total number of women participating in the study

most subjects were women (71%). Table 4 shows a complete description of baseline characteristics.

At the screening visit, the mean FEV_1 before the bronchodilator was 1.922 L (66.31% of the normal predicted value) and the mean FEV_1 after the bronchodilator was 2.393 L (82.56% of the normal predicted value). The mean reversibility of the FEV_1 was 470.60 mL (25.38%).

Cardiovascular risk factors were reported in 49 subjects (25%), including hypertension (n = 43;

22%), hyperlipidemia (n = 10; 5%) and diabetes (n = 9; 5%). During the study, 106 participants (53%) received one concomitant drug or more. Analgesics, antihypertensives and antihistaminics were the most frequently prescribed drugs.

Treatment compliance was at least 80% for most participants (188/191 subjects [98.4%] for the Neumoterol® 400 capsule and 183/187 subjects [97.8%] for the RMP). The median of compliance was within the 94%-97% range for both formulations during each treatment period.

Efficacy results: The primary efficacy endpoint was the change in trough FEV_1 in the morning of day 29, compared to the baseline value. In both treatments, there was an increase in the morning trough FEV_1 in the ITT population. The mean increase in the least squares (LS) adjusted to the model was 0.194L for Neumoterol® 400 and 0.150 L for the RMP. The non-inferiority of the Neumoterol® 400 capsule (BFF 400/12 μg) was demonstrated: the lower limit of the 95% confidence interval (CI) for the treatment difference was higher than the predetermined non-inferiority margin of –125 mL (difference of 0.044 L; 95% CI: –0.008; 0.096) (Figure 3).

One analysis carried out in the PP population was similar to the primary analysis of the ITT population. The non-inferiority of the Neumoterol® 400 capsule (BFF 400/12 μg) was evidenced when compared with the RMP (BFF 320/9 μg) (treatment difference: 0.043 l; 95% CI: –0.012; 0.098).

There was an improvement in trough FEV_1 in both treatments from the baseline period until day 29 of period 1 (from visit 2 to visit 3) and from the baseline period until day 29 of period 2 (from visit 4 to visit 5). Whereas the trough FEV_1 decreased during the washout period of 4 weeks between periods 1 and 2, it remained above the baseline value before treatment (that is to say, the mean trough FEV_1 in the baseline period for period 2 [visit 4] was barely higher than the level observed during

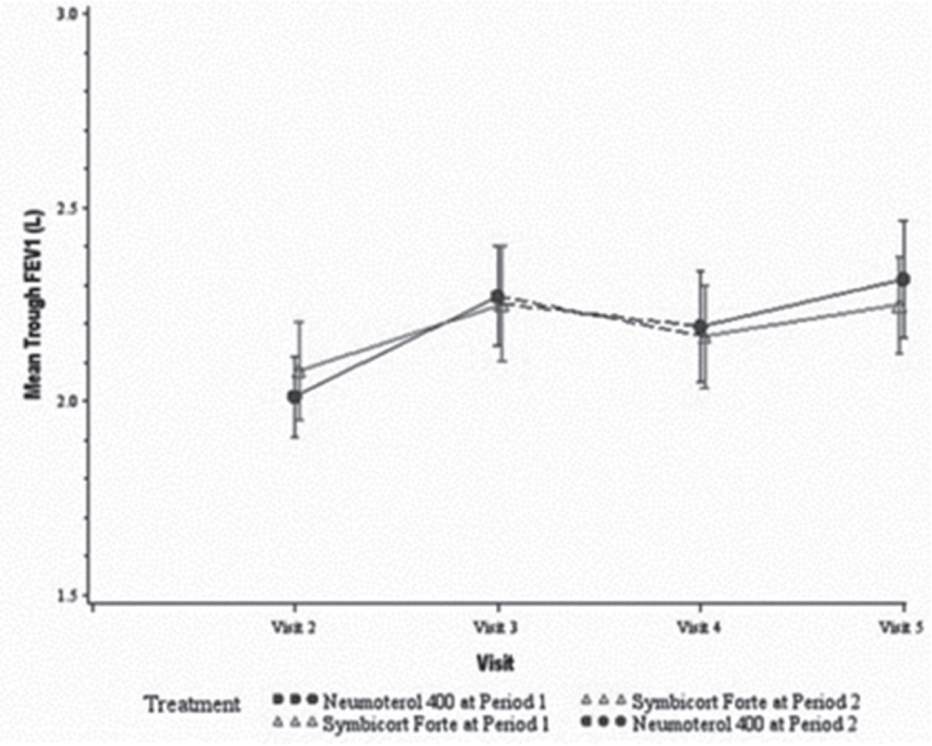

Figure 3. Mean of trough FEV1 (L) and 95% CI at each study visit, per treatment (ITT population).

the baseline period for period 1 [visit 2], regardless of the treatment).

The $AUC_{0\text{-}10\ h}$ of the FEV_1 at the beginning of each treatment period was a secondary efficacy endpoint. In the ITT population, the $AUC_{0\text{-}10\ h}$ of the FEV_1 on day 1 was 0.98 L*h (95% CI: 0.576; 1.384) higher for Neumoterol® 400 (BFF 400/12 μg) (Figure 4).

In the ITT population, both treatments were associated with an increase in the ACT score (another secondary efficacy endpoint) from the baseline period until day 29. The mean increase in the LS adjusted to the model was 1.6 points for Neumoterol® 400 (BFF 400/12 μg) and 1.0 point for RMP (BFF 320/9 μg). This treatment difference favored the BFF 400/12 μg capsule, since there was a difference of 0.6 points (95% CI: 0.1; 1.1).

Safety results: AEs were reported during treatment in 33 patients (17%) of the group receiving the BFF 400/12 μg capsule and 37 subjects (19%) of the group who received BFF 320/9 μg. Post-treatment AEs were reported in 17 (9%) and 22 (11%) participants, respectively. AEs (either during or after treatment) were reported in 47 subjects (24%) for the BFF 400/12 μg capsule and 51 patients (26%) for BFF 320/9 μg. There wasn't any statistically significant difference regarding the incidence of at least one AE neither during nor after treatment between both treatment groups (probability index: 0.8875; 95% CI: 0.510; 1.544) (Table 5). No deaths were reported, and none of the female participants got pregnant during the course of the study.

One serious AE was reported during treatment in the BFF 400/12 μg capsule group (cholelithiasis), and one serious AE was reported during treatment in the BFF 320/9 μg group (rash), which led to the definitive discontinuation of the study drug. The investigator didn't think those serious AEs were associated with the study drug. No post-treatment SAEs were reported. None of the subjects interrupted the treatment or discontinued the study due to pre- or post-treatment AE in the BFF 400/12 μg capsule group. The most frequently reported AEs during treatment are summarized in Table 6. AEs reported in at least 2% of the participants of any of the groups were: headache (4% and 3%, respectively), rhinitis (2% and 3%) and bronchitis (1% and 3%).

The most frequently reported post-treatment AEs were infections and infestations (4% for Neumoterol® 400 [BFF 400/12 μg] and 5% for the RMP [BFF 320/9 μg]), nervous system disorders (1% and 4%, respectively), gastrointestinal disorders

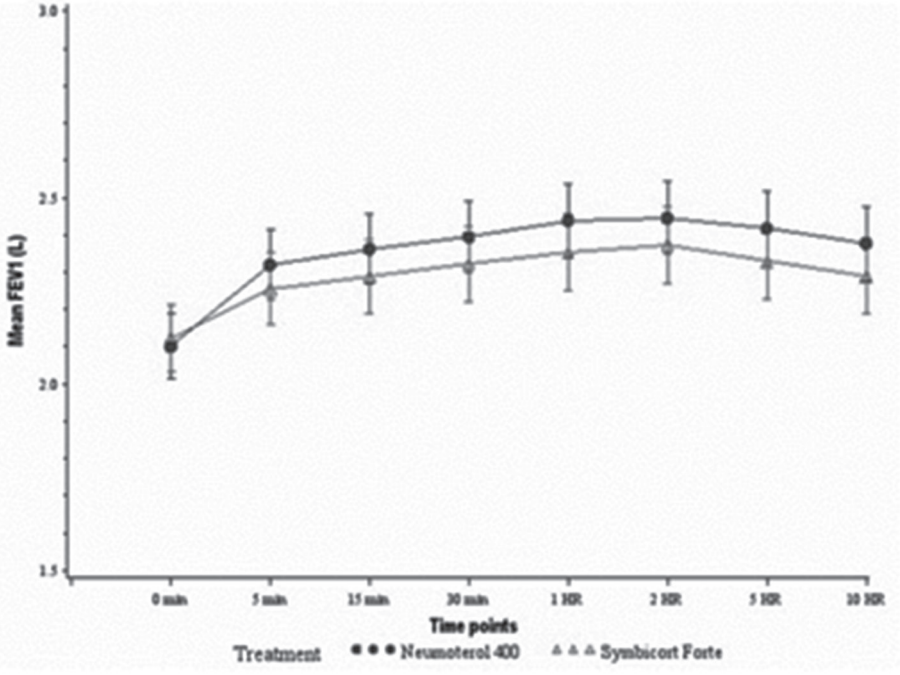

Figure 4. Mean of serial FEV1 and 95% CI at each time point (ITT population).

TABLE 5. General considerations of AEs

	Neumoterol® 400 BFF 400/12 µg capsule (n = 193) n (%)	RMP BFF 320/9 µg dry powder (n = 194) n (%)
AEs during treatment		
Any AE	33 (17)	37 (19)
AE related to study treatment	2 (1)	0
AE derived from definitive discontinuation of the study drug or study withdrawal	0	1 (1)
Any AE	1 (1)	1 (1)
SAE related to study treatment	0	0
Fatal SAE	0	0
Fatal SAE related to study treatment	0	0
AEs after treatment		
Any AE	17 (9)	22 (11)
AE related to study treatment	1 (1)	0
AE derived from definitive discontinuation of the study drug or study withdrawal	0	0
Any AE	0	0
SAE related to study treatment	0	0
Fatal SAE	0	0
Fatal SAE related to study treatment	0	0
AEs during or after treatment		
Any AE	47 (24) (*)	51 (26) (*)
AE related to study treatment	3 (2)	0
AE derived from definitive discontinuation of the study drug or study withdrawal	0	1 (1)
Any AE	1 (1)	1 (1)
SAE related to study treatment	0	0
Fatal SAE	0	0
Fatal SAE related to study treatment	0	0

(*) Difference compared to RMP (BFF 320/9 µg): probability index of 0.8875 (95% confidence interval: 0.510-1.544).
In each level of the patient's summary, he/she was counted only once if he/she reported one or more AEs. SAE: serious adverse event.

TABLE 6. AE más frecuentes (≥ 2 %) durante el tratamiento según la clase de sistema y órgano (población de seguridad)

System organ class Preferred term	Neumoterol® 400 BFF 400/12 µg in capsules (n = 193) n (%)	RMP BFF 320/9 µg in dry powder (n = 194) n (%)
Any AE during treatment (*)	33 (17)	37 (19)
Infections and infestations	15 (8)	23 (12)
Rhinitis	4 (2)	6 (3)
Bronchitis	2 (1)	5 (3)
Nervous system disorders	9 (5)	5 (3)
Headache	8 (4)	5 (3)
Gastrointestinal disorders	3 (2)	5 (3)

(*) AEs were coded using version 18.1 of the MedDRA.

(2% and 2%), and musculoskeletal and connective tissue disorders (2% and 0%). Headache was the only post-treatment AE; it was reported by at least 2% of subjects (2% for BFF 400/12 μg and 0% for BFF 320/9 μg).

The investigator considered that two AEs during treatment (palpitations and headache) and 1 AE after treatment were associated with the BFF 400/12 μg capsule. None of the AEs during or post-treatment were considered to be associated with BFF 320/9 μg.

Two subjects (1%) showed moderate asthma exacerbation during treatment with BFF 400/12 μg. One participant (1%) showed moderate asthma

exacerbation during treatment with BFF 320/9 μg. All these asthma exacerbations were resolved after medical intervention. One patient showed moderate asthma exacerbation after treatment, at the end of the BFF 320/9 μg treatment period, which was resolved.

No clinically relevant differences were reported between the two treatments in the central tendency for clinical biochemistry values at the baseline period or on day 29, and no changes were reported, either, from the baseline period until day 29, including glucose and potassium levels. No differences were observed between the treatments in terms of changes in the arterial pressure or duration of the QT interval from pre-dose until 30 min post-dose on day 29.

There was a small increase in the heart rate, from pre-dose until 10 min post-dose on day 29 for BFF 400/12 μg (mean increase in the LS of 1.3 beats/min), whereas the heart rate for BFF 320/9 μg remained essentially invariable. This difference between treatments regarding the change in the heart rate was statistically significant (difference: 1.2 beats/min; 95% CI: 0.1; 2.3). The difference was temporary, and there weren't any differences between the BFF 400/12 μg capsule and BFF 320/9 with respect to the change in the heart rate from pre-dose until 30 min post-dose on day 29 (difference: 0.2 beats/min; 95% CI –0.7; 1.2). No tachycardia events were reported during the study, but one participant had an AE of mild palpitations 3 d after the beginning of treatment with the BFF 400/12 μg capsule. No differences were observed between the two treatments in terms of changes in systolic or diastolic arterial pressure from pre-dose until 30 min after dose on day 29.

Exploratory endpoint: The subjects' preference on the use of the devices at the end of each treatment period was defined as an exploratory endpoint. A higher proportion of subjects said that Neumoterol® 400 (BFF 400/12 μg) was "very comfortable to use" compared to the RMP (BFF 320/9 μg), (41% versus 27%, respectively), and "very easy to use" (44% versus 25%), and felt very confident that they had used the medication satisfactorily (41% versus 21%). In general, more participants expressed their preference for the Neumoterol® 400 (BFF 400/12 μg) inhaler, 50% versus 32%. Table 7 provides a detailed description.

TABLE 7. Patient's preference on the use of the devices (exploratory endpoint) at the end of each treatment period (ITT population)

	Neumoterol® BFF 400/12 µg (n = 193) n (%)	RMP BFF 320/9 µg (n = 194) n (%)
How comfortable do you think it is to inhale the drug through an inhaler?		
Very comfortable	79 (41)	52 (27)
Comfortable	97 (50)	97 (50)
Moderately comfortable	8 (4)	25 (13)
Uncomfortable	2 (1)	12 (6)
Very uncomfortable	1 (1)	2 (1)
How simple do you think it is to use the inhaler?		
Very simple	84 (44)	48 (25)
Simple	96 (50)	104 (54)
Moderately simple	7 (4)	29 (15)
Difficult	0	6 (3)
Very difficult	0	1 (1)
How sure are you that you have taken the drug correctly?		
Very sure	80 (41)	41 (21)
Sure	99 (51)	79 (41)
Moderately sure	8 (4)	31 (16)
Unsure	0	33 (17)
Very unsure	0	4 (2)
Which inhaler would you rather use every day?		
BFF 400/12 µg capsules	54 (28)	42 (22)
BFF 320/9 µg in Turbuhaler®	21 (11)	41 (21)
No preference	16 (8)	9 (5)

DISCUSSION

Asthma is a serious worldwide health problem. There is increasing asthma prevalence in many countries, especially in pediatric populations. This disease imposes an unacceptable burden on healthcare systems and loss of work productivity.[2]

This phase IV study demonstrated the non-inferiority of the efficacy of a BFF 400/12 μg capsule inhaler (Neumoterol® 400) in comparison with the RMP (BFF 320/9 μg) administered twice daily in asthmatic adults. BFF 400/12 μg (Neumoterol® 400) showed improvements in the parameters of the pulmonary function and symptom control at the end of the 4-week treatment period.

It is important to mention that no difference was reported between the two treatments in terms of incidence of AEs or SAEs, neither during treatment nor after the treatment. In general, the safety profile of both treatment strategies was similar to the one reported before for BFF.[10] Two serious AEs were reported, but none of them was considered to be associated with the study drug.

No difference was reported between the two treatment strategies regarding the change from the baseline period until day 29 in pre-dose heart rate, pre-dose arterial pressure, pre-dose QTc, or the glucose or potassium levels.

It is interesting to highlight the fact that an exploratory evaluation of the patients' preference on the use of the devices showed that a higher proportion of subjects expressed global preference for the BFF 400/12 μg capsule in comparison with the inhalation of the RMP with BFF 320/9 μg (50% versus 32%, respectively). Few studies evaluated the preference of patients diagnosed with asthma or COPD[11] with regard to inhalation devices. This aspect represents a key factor in the improvement of treatment compliance.

This study has some limitations: The fact that this is an open-label study could be considered a weakness, but, to conduct a blind study with drugs administered through inhalation where the device is not interchangeable is not possible. For that reason, in order to improve the sensitivity of the study, a crossover design was used instead of a parallel study. Furthermore, the open-label modality also allowed the exploratory assessment of the patient's preference on the type of device.

Other limitations: randomization per center and the performance of non-centralized spirometries with comparable yet different equipment, according to each center.

CONCLUSIONS

The non-inferiority of Neumoterol® 400 (BFF 400/12 μg) evaluated in asthmatic adults was demonstrated, compared to the RMP (BFF 320/9 μg). A favorable tendency was observed with BFF 400/12 in the improvement of the pulmonary function on day 1 (AUC 0-10 FEV_1) and in symptom control (ACT) on day 29.

Both formulations were well-tolerated, and their safety profile was congruent with previous investigations. No serious AEs were reported in association with the study drug. A minimum (though statistically significant) change was described in the heart rate from pre-dose until 10 min post-dose on day 29, which was bigger for the BFF 400/12 μg capsule compared to the RMP BFF 320/9 μg; however, this difference in the heart rate change was transitory and was no longer observed after 30 min (difference: 0.2 beats/min; 95% CI –0.7; 1.2). A higher proportion of patients expressed global preference for the Neumoterol® 400 capsule (BFF 400/12 μg). We believe that the study results generate new clinical evidence of the safety and efficacy of this formulation, so heavily used in Argentina.

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